

Proposed collaboration: Genetic risk and progression to dementia in Parkinson's disease.

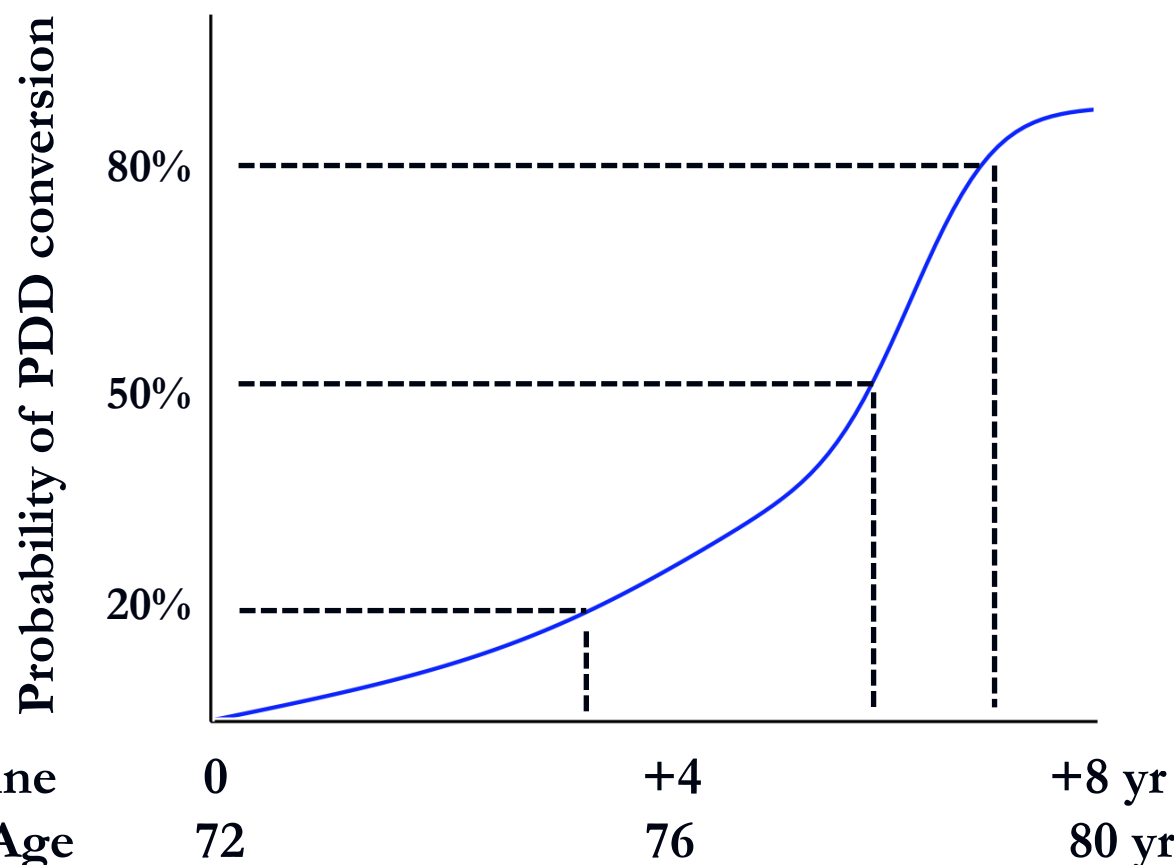
New Zealand Brain Research Institute
and
Medical Genetics, UBC, Canada



John Dalrymple-Alford, Tim Anderson,
Matt Farrer, and colleagues.

Objective: Time to PDD is a top priority. Establish a model, generated from a genetic risk score + other key factors, to estimate the probability of conversion to PDD over time: That is, an individualised probability, over time, expressed for each patient.

Output from Model - cumulative probability of PDD over time



Daniel Myall:

Bayesian regression, with multiple imputations for missing data, and out-of-sample prediction error determined using cross-validation.

Example is for 72y PD with “MCI” at baseline.

The aetiology of PDD, like PD, is multifactorial.

Hence four key risk factors will be examined:

- Age at assessment(s) (timepoint for interpreting motor and cognitive scores; not age at PD onset);
- Motor phenotype (akinetic-rigid; tremor);
- Poor cognition (eg. PD-MCI) is clearly a major risk factor;
- Genetic risk → global model, but also comparison of risk factors.

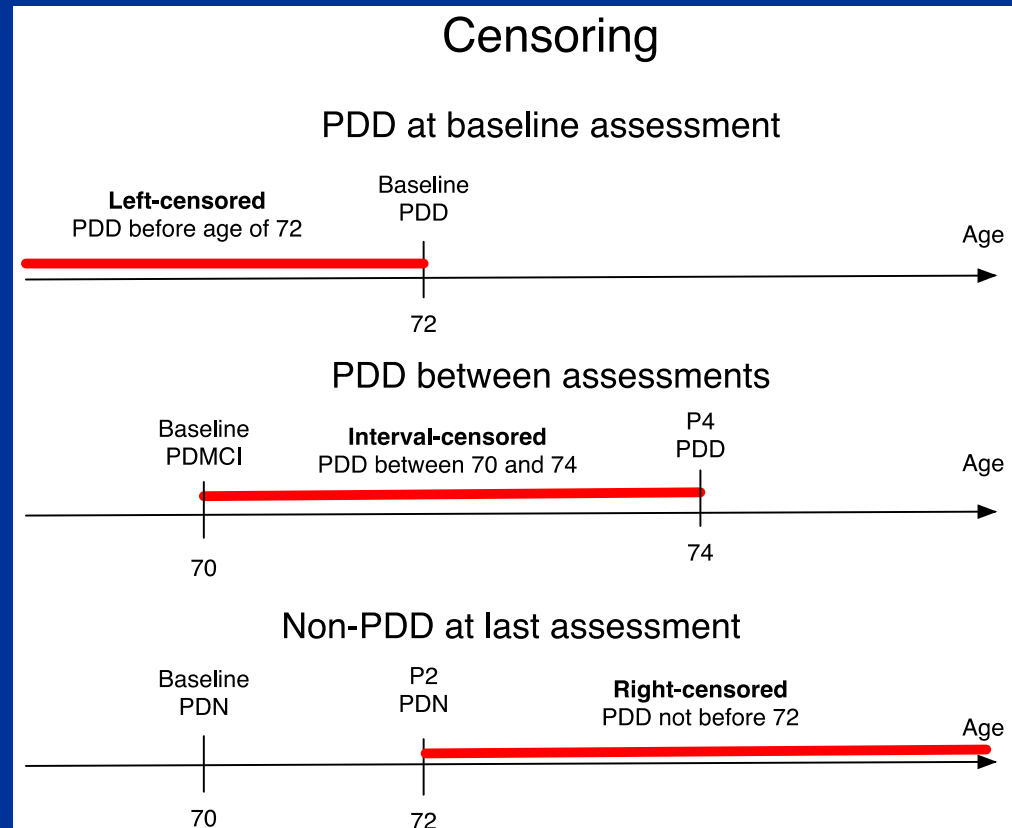
Novelty:

- Addition of a genetic risk score, based primarily on relevant variability in the alpha-synuclein gene (SNCA);
- Generation of a cognitive risk score, which may improve the predictive value of “MCI” and circumvent some of the problems of different test usage;
- Improved knowledge of expected disease course / patient care;
- Better intervention trials and analysis (targeted sample selection; genetically-based treatments / influences on response to therapy).

Non-genetic data will include both information at baseline and ALL other available points longitudinally:

- Conversions to PDD add more to model prediction, but it will benefit from inclusion of PDD at baseline and those who do not convert at last assessment. That is, it does not rely entirely on PDD conversion or avoid PDD status at baseline.

PDD at baseline and Non-PDD at end is useful info, bc this adds info to the model (eg. partic gene score is associated with PDD or not for a given age). Two or more assessments contribute more.

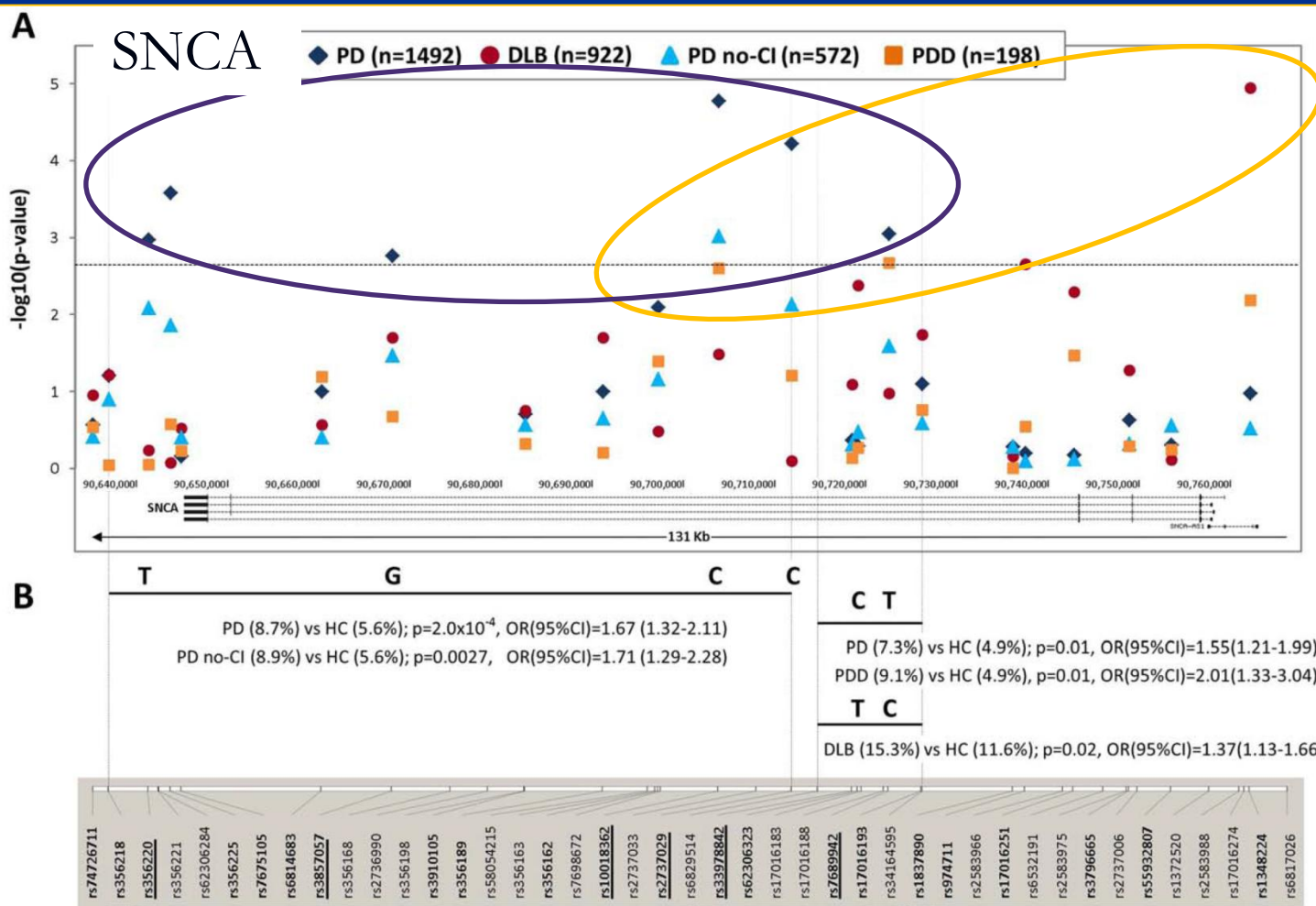


Genetic Risk: Variability in SNCA gene exists in sporadic Lewy Body diseases (Guella...Farrer, 2016; Annals of Neurology).

SNCA: confers the highest population-attributable risk of PD (GWAS).

Method: Single nucleotide resolution analysis (43 SNPs).

3' end, PD vs 5' end, PDD/DLB; Intron4 haplotypes of PDD/DLB differ.



Histone /
epigenetic
modifications in
Intron 4?

APOE status?

MAPT?

GBA?

Single risk score
derived from
Classification
And Regression
Tree Analysis.

Cognitive Risk Score:

- Clearly, collaboration will make this project more viable, and – if agreed – we propose joining with other sites, espec PD-MCI sites initially (Amsterdam, Chicago, others; +PPMI).
- All cognitive scores can be added at the time of model building, nested within site.
- This means that site differences in particular Neuropsych measures do not matter – the optimal measures predicting PDD will be identified, per site, for cognitive risk (better if some overlap).
- This can also be generated independently to reveal within-site measures sensitive to conversion to PDD, and should be similar to the global model based on all 4 primary risk scores examined simultaneously (we are in the process of doing this for NZBRI data, as shown on the next two slides).

NZBRI: Tests across 5 Cognitive Domains

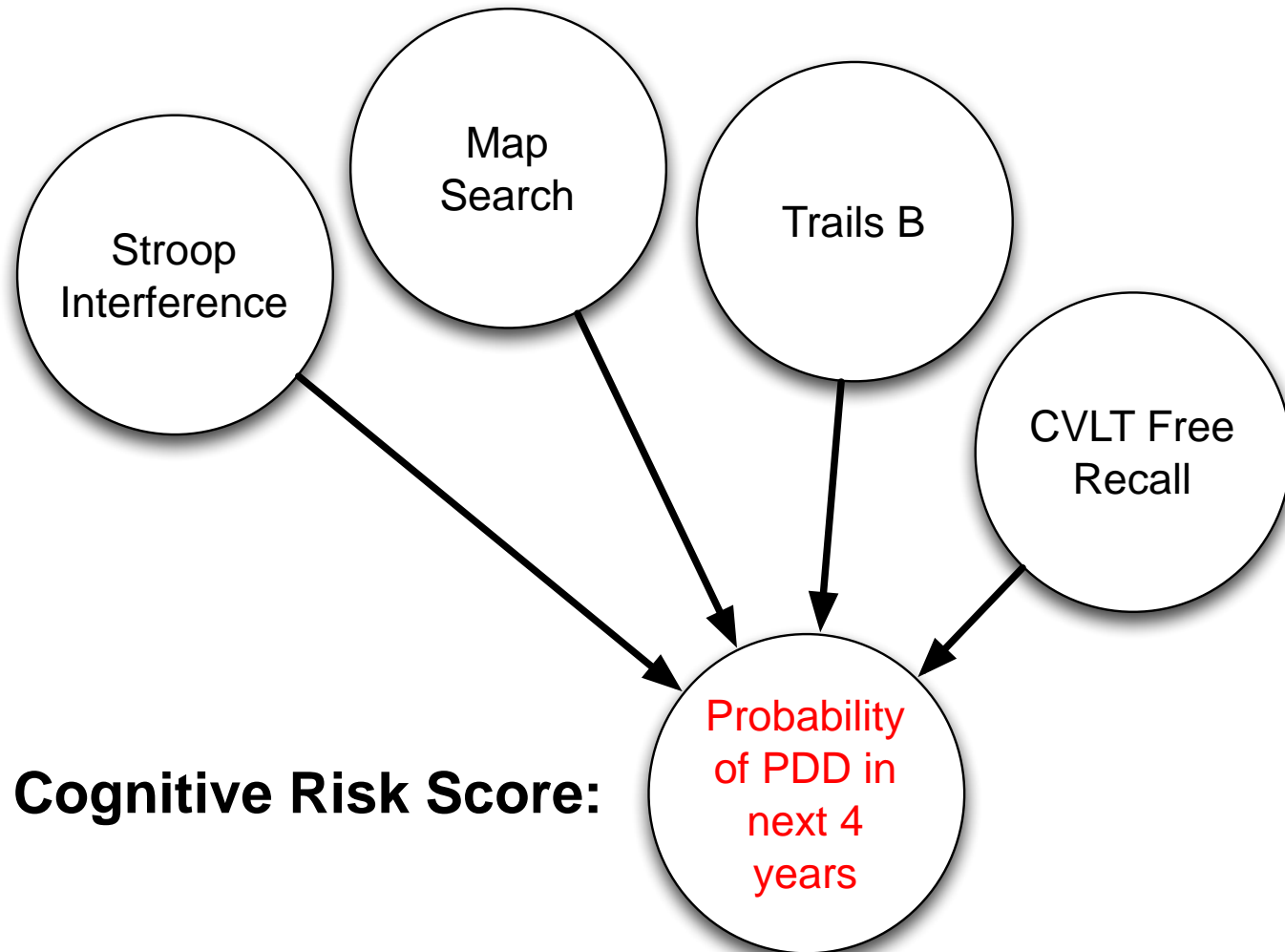
| Attention, Working Memory and Processing Speed | Executive Function | Visuoperceptual / Visuospatial | Learning and Memory | Language |
|---|------------------------------------|---|------------------------------------|-------------------------|
| Digits Forward/ Backward | Action (Verb) Fluency | Judgment of Line Orientation | CVLT-II SF acquisition | Boston Naming Test |
| Digit Ordering | Letter Fluency | Fragmented Letters | CVLT-II SF Short Delay (30secs) | Similarities (DRS-2) |
| Map Test (Test of Everyday Attention) | Category Fluency (D-KEFS) | Rey Complex Figure Copy | CVLT-II SF Long Delay (10mins) | Language (ADAS- COG) |
| Stroop Color Reading | Category Switching (D- KEFS) | Picture Completion | Rey – Short Delay (3mins) | |
| Stroop Word Reading | Trails B | ? | Rey – Long Delay (30mins) | |
| Trails A | Stroop Interference (D-KEFS) | ? | ? | |

NZBRI: Optimal tests for predicting PDD from our initial cohort

Gaussian process with regularisation for selecting tests and generating risk scores.

Maximise marginal likelihood to achieve good out-of-sample prediction performance. Checked by cross validation.

Can handle datasets with different sets of tests and generate comparable cognitive risk scores that can then be combined into a single analysis.



Collaborations sought and possible extensions:

- Coordinate through Gert and MDS PD-MCI consortium.
- Initially, patients already processed by Matt Farrer and Ilaria Guella's team. (Amsterdam; Chicago, NZBRI sites; n = 328).
- *Funding - Apply to NZ-Health Research Council, Fox, +?

Extensions:

- (1) Validation: NZBRI has ~+100 extra PD; other sites? Level 1 data from PPMI +?; validate the model's predicted conversions in current / new patients over time.
- (2) Neuroimaging: Association with composite / component PDD risk score (PDD-patterns: structural MRI; resting state networks; PET scans).
- (3) Tx trials (eg. do cognitive/exercise efficacy / outcomes vary with composite / component risk score in ongoing / future trials?).
- (4) Progression to MCI / genetic associations with MCI.

....Thank you for your time...